BAD TO THE BONE

Latest osteoporosis therapies offer alternatives for prevention and treatment

Osteoporosis continues to be underrecognized and undertreated in postmenopausal women, despite its prevalence and debilitating effects on their health. According to the National Osteoporosis Foundation (NOF), as many as eight million American women have osteoporosis and another 22 million women have bone density deficiency, putting them at risk for bone fracture and associated complications.

Fortunately, drugs approved recently or approaching approval arm women and their healthcare providers with new weapons against this disease. For their part, pharmacists can raise awareness within their communities about osteoporosis, work with the clinical team to identify the appropriate therapeutic regimen for each individual, and counsel patients about their new medications.

A novel approval for treatment

In late 2002, the Food & Drug Administration approved teriparatide

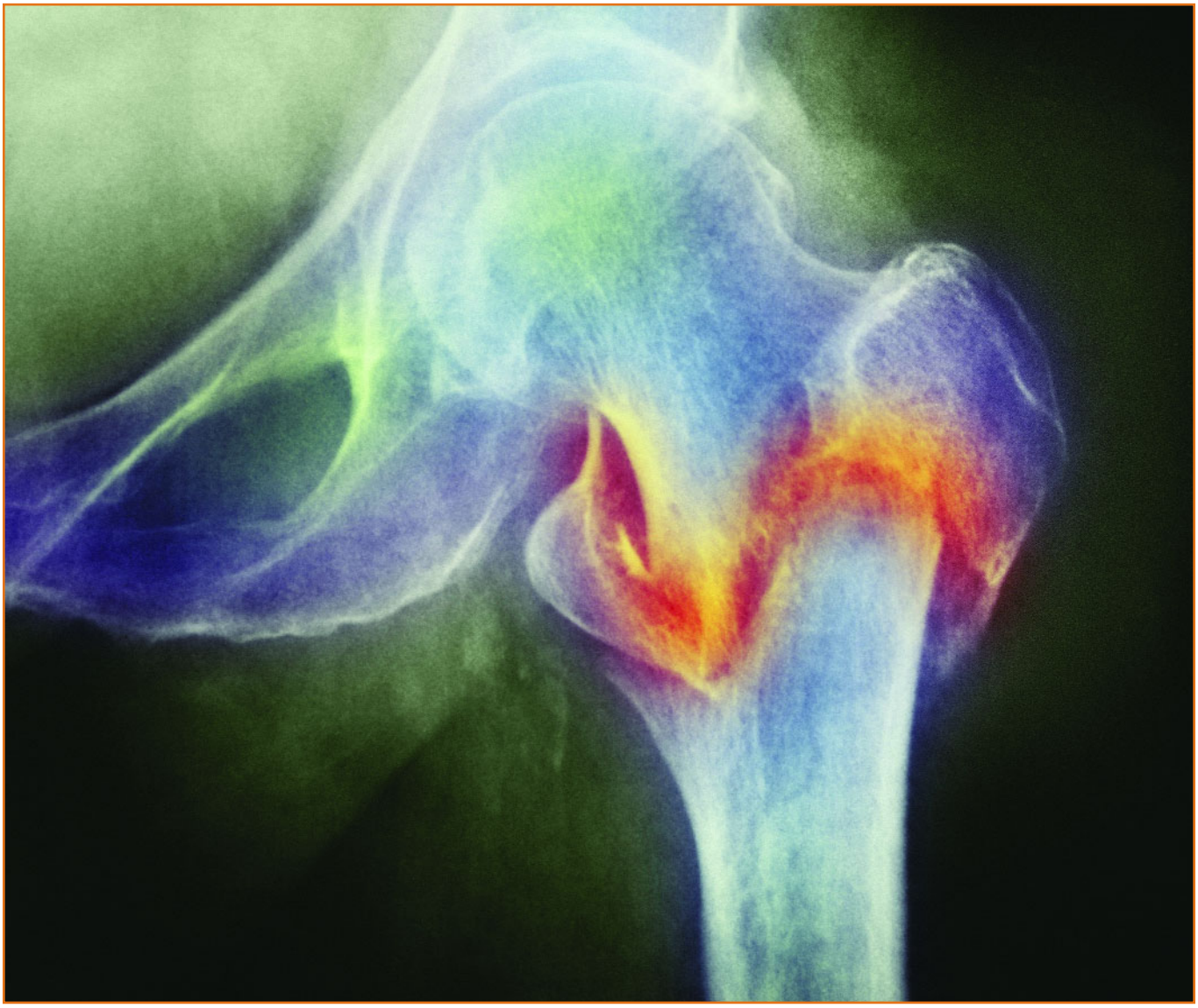


Photo: © Princess Margaret Rose Orthopaedic Hospital / Photo Researchers, Inc.

(rDNA origin) injection (Forteo, Eli Lilly), a recombinant form of human parathyroid hormone (PTH), for the treatment of postmenopausal women with osteoporosis who are at increased risk for fracture (see *Drug Topics*, Jan. 6, 2003).

Teriparatide is the first in a new class of drugs known as bone formation agents, which stimulate osteoblasts. These agents act to build bone, not to prevent bone loss. It is administered as a once-daily subcutaneous injection into the thigh or abdominal wall. The manufacturer recommends that teriparatide be given only to those women at high risk for osteoporotic fractures. These include women with a history of osteoporotic fracture, those who have multiple risk factors for fracture, or those who have failed or were intolerant of previous osteoporosis therapy.

Just approved for prevention

Clinicians will soon be able to offer postmenopausal women transdermal estrogen therapy that adequately protects the skeleton with half the dose of the lowest currently available estrogen. In June, the FDA approved estradiol transdermal system (Menostar, Berlex) 14 mcg per day for the prevention of postmenopausal osteoporosis (see *Drug Topics*, July 12). The product will be available later this summer.

Menostar differs from standard hormone replacement therapy in three ways, said Bruce Ettinger, M.D., a clinical professor of medicine at the University of California at San Francisco and the lead investigator for the clinical trial that led to the approval of Menostar. It delivers approximately 25% of the standard dose of estrogen, and does not require a concomitant daily or monthly progestin, he said. In addition, Menostar's transdermal route of administration avoids the "first-pass effect" in the liver, a potential cause of clotting problems.

Menostar is intended as long-term maintenance therapy for women 60 years of age or older who want osteoporosis prevention with a minimal likelihood of side effects or tolerance issues, Ettinger continued. He pointed out that it is not intended for use as hormone replacement therapy in young women who have had their ovaries removed or in very symptomatic menopausal women.

According to Ettinger, Menostar is remarkable in terms of its tolerability. He reported that in the clinical trial, the incidence of adverse effects usually associated with hormone therapy, such as bleeding, breast tenderness, and headache, were similar for both the Menostar and placebo groups. The reason Menostar has such as excellent tolerability profile is that it does not aim to restore estrogen to youthful levels, it only aims to increase estrogen to age-expected levels, he explained.

What's in the pipeline?

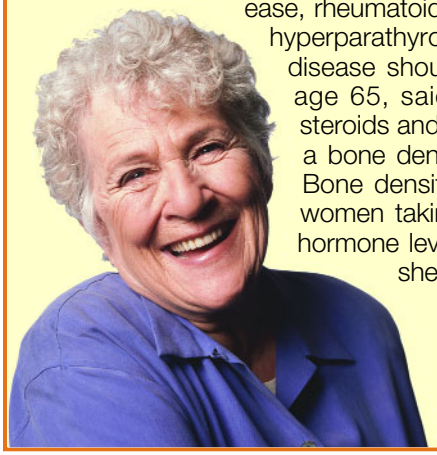
Within the next several years, six key drugs for the treatment of osteoporosis should become available in the United States. Ibandronate (Boniva, Hoffmann-La Roche), an oral bisphosphonate that is taken monthly, should reach the market in the near future, said Ethel Siris, M.D., the Madeline C. Stabile professor of clinical medicine at Columbia University College of Physicians and Surgeons and director of the Toni Stabile Osteoporosis Center at New York Presbyterian Hospital. A once-daily oral version of the drug has received FDA approval. However, Roche and its partner, GlaxoSmithKline, have delayed marketing this dose and are currently investigating monthly oral and quarterly intravenous dosing regimens.

According to Roche, a supplemental New Drug Application (NDA) for once-monthly oral ibandronate was submitted to the FDA in May and is currently under review. The company recently announced the

Who should get screened?

All women 65 years of age and over should have a bone density scan, said Felicia Cosman, M.D., clinical director of the National Osteoporosis Foundation. Women who are younger than 65, but who are postmenopausal, should have a bone density scan if they have certain risk factors for osteoporosis, such as if they are a smoker, if they weigh less than 127 lb. (unless they are very petite), if they have a prior fracture in the absence of major trauma, or if they have a familial history of fracture or osteoporosis.

In addition, women with conditions such as inflammatory bowel disease, rheumatoid arthritis, endocrine diseases such as hyperparathyroidism or hyperthyroidism, and celiac disease should have a bone density scan before age 65, said Cosman. Women taking corticosteroids and thyroid medications should also have a bone density scan before age 65, she added. Bone density testing is particularly important for women taking thyroid medications if their thyroid hormone levels are not being carefully monitored, she cautioned.



Cosman named the following as additional risk factors for osteoporosis: low calcium intake, excessive alcohol consumption, sedentary lifestyle, and Caucasian or Asian ethnicity.

Photo: PhotoDisc

Making an ImPACT on osteoporosis

The American Pharmacists Association Foundation recently launched an initiative called Project ImPACT: Osteoporosis, based on a previously successful hyperlipidemia program, said Jean-Venable "Kelly" Goode, Pharm.D., an associate professor at the School of Pharmacy at Virginia Commonwealth University in Richmond. The APhA Foundation, with support from Merck, partnered with Ukrop's Super Markets in Richmond to launch the demonstration project on a regional basis.

Goode, who was lead author of the study, said that the objectives of the initial phase of the project were to identify those at risk for osteoporosis through pharmacy-based screening, to refer at-risk patients to a physician for further evaluation and treatment, and to follow up with these patients.

Of the 532 patients who were screened for osteoporosis, 70 were found to be at moderate or high risk for the disease, and 78% indicated that they had no prior knowledge of their relative fracture risk, Goode reported. Of those in the moderate- or high-risk categories, 37% scheduled and completed a physician visit, 19% had a diagnostic scan, and 24% of those patients were initiated on osteoporosis therapy subsequent to the screening.

Based on these findings, the investigators concluded that pharmacists could play a useful role in the identification, education, and referral of patients at risk for osteoporosis through pharmacy-based BMD screening, said Goode. The researchers also found that patients were willing to pay out-of-pocket for the screening service, she said. In this instance, those screened paid a fee of $25 for the service.

The APhA Foundation and its partner, Ukrop's Super Markets, presented these findings to convince UnitedHealthcare of the Mid-Atlantic, a regional payer, to compensate participating pharmacists approximately $1 to $2 per minute for the collaborative community health management services provided to its members enrolled in the project.

findings of a phase III study (the Dosing IntraVenous Administration, or DIVA, study) that suggest intravenous ibandronate and daily oral ibandronate possess equal ability to increase vertebral bone mineral density (BMD).

Zoledronic acid, or zoledronate (Zometa, Novartis), is another bisphosphonate currently in late-stage clinical trials for the treatment and prevention of osteoporosis. It was previously approved for the treatment of patients with hypercalcemia of malignancy, multiple myeloma, and documented bone metastases from solid tumors, Siris said. The drug would be dosed as a 5-mg once-yearly intravenous infusion, she added, while pointing out that a 4-mg infusion is used in cancer patients.

Siris said that the idea of a once-yearly formulation of zoledronic acid has generated a lot of excitement among clinicians and their patients. For some women, including those in nursing homes or assisted-living facilities or those who are taking many other medications, a once-yearly IV infusion could be a terrific way to go, she said.

Little information is available about the selective estrogen receptor modulators (SERMs) lasofoxifene (Pfizer) and bazedoxifene (Wyeth), because studies are still ongoing, Siris said. However, phase II data suggest that BMD continues to increase after 24 months of therapy with lasofoxifene, she reported.

Wyeth reports that bazedoxifene is in trials both as monotherapy and in combination with conjugated estrogens (Premarin) tablets. Concluded Siris, "I suspect both SERMs will effectively prevent bone loss, but the real issue is getting robust data from the ongoing clinical studies demonstrating a reduction in fracture risk in those with osteoporosis."

New anabolic agents

Novel bone-forming drugs represent a promising approach to increasing BMD and reducing osteoporotic fracture risk. In the final stages of development and testing are recombinant human PTH (Preos, NPS Pharmaceuticals) and strontium ranelate (Protelos, Servier). Both NPS and Servier recently reported results from phase III trials, and both companies are expected to file NDAs before the end of the year.

Preos is a full-length recombinant version of the hormone from which teriparatide is also derived, Siris explained. She said that NPS Pharmaceuticals held a press conference with its investors, where it presented results indicating that Preos reduces vertebral fracture risk, but not much information regarding the product's effect on nonvertebral fracture risk. More data are needed to help clinicians better assess Preos' safety, tolerability, and efficacy, and these data should be available soon, she said.

Strontium is a very interesting compound, said Siris. In European studies, it has demonstrated an ability to reduce vertebral fracture risk. In addition to being slightly anabolic, it has a mild antiresorptive effect, she noted.

So, what else is new?

Other therapies for osteoporosis are in the pipeline as well. Warren Levy, Ph.D., president and CEO of Uni-

gene Laboratories, Fairfield, N.J., said that the company has developed a nasal calcitonin product, Fortical, that has certain advantages over the existing product in terms of reduced manufacturing and packaging costs. According to the Unigene Web site, the company received an FDA approvable letter for this product in January and the agency is currently reviewing the NDA.

In 2002, Unigene signed a $150 million worldwide license agreement with GlaxoSmithKline for the development of an oral formulation of PTH for the treatment of osteoporosis, Levy said. In June, Unigene announced that it would receive a $4 million milestone payment from GSK for the commencement of phase I clinical trials of this PTH product. In addition, the company has developed an oral calcitonin product that has completed phase I/II clinical testing.

Felicia Cosman, M.D., clinical director of NOF, said that other drugs in development for the prevention and treatment of osteoporosis include growth hormones and growth hormone derivatives. Statins are also being evaluated as a treatment for osteoporosis, added Cosman, who is an endocrinologist specializing in osteoporosis at Helen Hayes Hospital, West Haverstraw, N.Y. Other researchers are searching for additional anabolic or bone-building drugs. Such therapies are far off, however. "These are things we'll hear more about in the future," she said.

The role of the pharmacist

The impending approval of these new medications puts pharmacists center stage, so to speak. Women must realize that they can talk to pharmacists about osteoporosis, because pharmacists keep abreast of the issues and are aware of the available therapeutic options, said Lindsey Stephens, R.Ph., senior manager for professional services at Medicap Pharmacies in West Des Moines, Iowa.

"Pharmacists are very accessible healthcare providers. As such, they can play a significant role in community health prevention, particularly in terms of osteoporosis," concurred Jean-Venable "Kelly" Goode, Pharm.D., an associate professor at the School of Pharmacy at Virginia Commonwealth University in Richmond.

Goode recommended opening up a dialogue with patients about osteoporosis. "One of the things I have found is that many patients have never broached the subject with their physician," she said. Very few physicians focus on prevention and wellness because they have such a limited amount of time with each patient, she explained. Pharmacists can identify those at risk for osteoporosis, and then get them screened and referred for appropriate care, she said (see box on page 31).

Once patients have been diagnosed with osteoporosis, they can be referred back to the pharmacist for medication therapy management services, said Goode. This may include educating patients about their disease, medication and adherence issues, and the importance of appropriate diet and vitamin supplementation.

In-store screening

Setting up a pharmacy-based osteoporosis screening program requires dedication, commitment, and investment, said Stephens, who oversees screening services at Medicap Pharmacies' franchise stores. She recommended that when pharmacists consider providing osteoporosis screening in their store, they first decide how often they want to offer this service, based on community demand.

If pharmacists plan to offer frequent screening, they may want to acquire their own screening machine, Stephens said. In pharmacies, the most popular method of BMD testing is using ultrasound BMD analyzers. These machines cost approximately $15,000, and are about the size of a medium-sized suitcase, said Goode.

If pharmacists plan to offer osteoporosis screening on an intermittent basis, or if they are unsure of community demand, a good way to gauge interest is to outsource screening, or perhaps rent the device, Goode suggested.

On the front lines

The issue of preventive care and wellness is beginning to gain momentum in the United States, said Goode, because the country will not be able to handle the chronic disease burden in the future. The Surgeon General is looking to pharmacists as frontline healthcare practitioners for help with wellness and prevention programs, involving cholesterol, blood glucose, and blood pressure screenings and vaccination programs, she said. Osteoporosis prevention is yet another issue to which pharmacists can draw attention, she concluded.

Charlotte LoBuono

Web sites of interest

- American Academy of Orthopaedic Surgeons and National Osteoporosis Foundation position statement on osteoporosis: **www.aaos.org/wordhtml/papers/position/1113.htm**
- BoneBalance: **www.bonebalance.org**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases: **www.niams.nih.gov/hi/topics/osteoporosis/hormones.htm**
- National Institutes of Health Osteoporosis and Related Diseases National Resource Center: **www.osteo.org**
- National Osteoporosis Foundation: **www.nof.org**